

As one of the Clinical Experts who participated in the Appraisal Committee Meetings, I welcome the opportunity of commenting on the NICE Appraisal Consultation Documents (ACDs) on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women.

General Comments

Sections 1 and 2.4: The bone mineral density (BMD) T score thresholds used in both Appraisal Consultation Documents relate to dual x-ray absorptiometry (DXA) measurements performed at the femoral neck. Lumbar spine BMD measurements are often performed at the same time, as some patients have osteoporosis at this site, which is not apparent at the proximal femur. Furthermore, the spine contains a greater proportion of metabolically active trabecular bone than the proximal femur, so is more useful for monitoring response to treatment. Although lumbar spine BMD measurements may be spuriously elevated in older women, because of aortic calcification, spondylotic changes and vertebral deformation, they may provide useful information, particularly in patients who have undergone bilateral hip surgery. Although femoral neck BMD measurements may be the preferred option for the diagnosis of osteoporosis and fracture risk assessment, I suggest that NICE guidance recognises the potential value of lumbar spine BMD, albeit with the caveats mentioned above.

Section 4.1.2: The anti-fracture efficacy of treatments has been estimated from pooled data, regardless of participants' age, baseline BMD and fracture status. Although there is less information on the efficacy of osteoporosis treatments in elderly women, studies show no apparent attenuation of benefit with advancing age. In contrast, previous studies suggest that reduction of clinical fractures with alendronate and risedronate only occurs in women with documented osteoporosis (Cummings et al, JAMA 1998; 280: 2077-2082 and McClung et al, N Engl J Med, 2001; 344:333-340). The calculated relative risk reduction from pooled data is therefore likely to underestimate the efficacy and cost-effectiveness of treatment in osteoporotic women.

Sections 1.1, 4.3.8 (Secondary Prevention) and 4.3.12 (Primary Prevention): The guidance arising from the two Technology Appraisals treats the three licensed bisphosphonates as a class, despite the lack of convincing evidence that cyclical etidronate reduces non-vertebral fractures. I accept that Section 1.2 highlights that in choosing which bisphosphonate to use, clinicians and patients need to balance proven effectiveness against tolerability and side-effects. Nevertheless, the current recommendations mean that cyclical etidronate is included as a first line agent, where strontium ranelate is relegated to a position as a second line agent, despite its proven efficacy at reducing the incidence of non-vertebral fractures.

Section 5.4 mentions that "strontium ranelate may interfere with the results of DXA scanning as it has similar properties to calcium". It would be more correct to state that strontium ranelate leads to large increases in BMD, but approximately 50% of this spurious, because of the higher atomic number of strontium than calcium. This leads

to further problems with the definition of non-response to treatment, where the artefactual increase in BMD with strontium will inevitably mean that patients fully adherent to treatment cannot fulfill the criterion of a decline in BMD.

Primary Prevention of Osteoporotic Fragility Fractures

Has all the relevant evidence been taken into account?

I welcome the development of the World Health Organisation (WHO) model for prediction of absolute fracture risk and appreciate the difficulties of incorporating this into NICE guidance, before the WHO algorithm is published. Nevertheless, I am concerned that the preliminary guidance has excluded current smoking and alcohol of >2 units/day from the WHO risk factors, "because their effects on fracture risk were relatively small, and such behavioural risk factors are difficult to confirm reliably". These have been shown to be reliable risk factors for fracture in large epidemiological studies, although Table 10 from the Evaluation Report suggests that their effect is smaller than other risk factors. Furthermore, as these risk factors are easy to identify in clinical practice, I feel that they should be incorporated in the guidance. It would also be useful to list the conditions other than rheumatoid arthritis, which the Appraisal Committee considers are associated with bone loss. This would avoid the potential for geographical variation in the interpretation and implementation of NICE guidance.

Are the Summaries of Clinical and Cost Effectiveness Reasonable Interpretations of the Evidence and are the Preliminary Views on the Resource Impact and Implications for the NHS Appropriate?

Section 4.2.14 indicates that a maximal acceptable figure of £20,000 per QALY gain was used for primary prevention, whereas the secondary prevention guidance has used a QALY threshold of £30,000. Although I appreciate the different philosophies underlying primary and secondary prevention, a vertebral or hip fracture is as devastating and costly if it is the first or subsequent fracture. For women at comparable risk of fracture, primary and secondary prevention are equally important. Using a different QALY threshold for primary and secondary prevention appears inequitable. Furthermore, osteoporotic women without fractures are not necessarily well and asymptomatic (section 4.3.9), as many already have other underlying conditions associated with substantial morbidity. Preventing osteoporotic fractures in this situation may reduce further impairment in quality of life.

Are the Provisional Recommendations of the Appraisal Committee Sound and do they Constitute a Suitable Basis for the Preparation of Guidance to the NHS?

Section 4.2.23 suggests that no women under the age of 70 years without a fracture can be identified and treated cost-effectively, although some women with very low BMD and other risk factors may be at high risk of fracture. Section 4.2.6 states that a 50-54 year old woman with a T score of -4.0 has the same absolute risk of fracture as a 75-79 year old woman with a T Score of -2.5. Denying younger women at high risk of fractures access to bone density measurement may be perceived as "Reverse Ageism". Although the costs of identifying patient suitable for treatment may be higher in younger than older women, many of the younger patients at high risk

already present to clinicians, because of inflammatory bowel disease, rheumatoid arthritis and other chronic conditions. I understand that glucocorticoid-induced osteoporosis will be addressed by the Clinical Guideline Development Group, but I am unclear if this group will tackle the management of younger women with other underlying causes of secondary osteoporosis.

The ACD preliminary recommendations mean that as fewer risk factors are needed to justify BMD measurement with advancing age, potentially large numbers of women over the age of 75 years with one or more risk factors for fracture will be referred for BMD measurements. If the proposed recommendations are followed uncritically, this could lead to the referral of older women with dementia and/or multiple medical problems, which overshadow any consideration of osteoporosis and fracture risk.

Secondary Prevention of Osteoporotic Fragility Fractures:

Although I welcome the updating of the secondary prevention Technology Appraisal to include strontium ranelate, I am disappointed that the opportunity for improvement of the existing guidance may have been missed.

Has all the relevant evidence been taken into account?

Section 1.6: The definition of an unsatisfactory response to treatment includes a further fracture despite full adherence to treatment for one year and evidence of a decline in BMD to below pre-treatment values. This implies that it is useful to measure BMD within a year of starting treatment, when previous research has suggested that measurements may be misleading (Cummings et al, JAMA. 2000 Mar 8; 283:1318-1321). A more appropriate definition of unsatisfactory response might be significant reduction in BMD over two years of treatment (with or without further fractures) or further fractures in the presence of a very low BMD.

I am also concerned about the restrictive recommendations on the use of teriparatide in patients with fractures and a very low BMD. Section 4.3.21 acknowledges that some women under the age of 65 years could be treated cost-effectively with teriparatide, if bisphosphonates and strontium were contraindicated. This would appear to be more appropriate than following the current guidance of using raloxifene.

Are the Provisional Recommendations of the Appraisal Committee Sound and do they Constitute a Suitable Basis for the Preparation of Guidance to the NHS?

Sections 1.1 and 7.3.3: I am still concerned that even in the revised guidance, a woman under the age of 65 years who already has a low trauma and documented osteoporosis, will be denied effective treatment, unless the T Score is lower than -3.0, or there is an additional risk factor present. This is particularly the case in women with an incident vertebral fracture, where there is a 20% risk of further fracture in the subsequent year.

Sections 1.4 and 7.3.6: The recommendations on the use of raloxifene appear particularly restrictive, limiting use to patients who are unable to tolerate

bisphosphonates or strontium ranelate. Although raloxifene does not appear to prevent non-vertebral fractures, it is clinically useful in the management of younger postmenopausal women, particularly those perceived to be at increased risk of breast cancer.

Sections 1 and 7.3.1: The use of bisphosphonates in the treatment of women above the age of 75 years without the need for DXA may expose some women unnecessarily to the side effect of medication. A recent audit from the Fracture Clinic at Newcastle General Hospital suggests that a third of women above the age of 75 years with an apparent low trauma fracture (excluding hip fracture) do not have osteoporosis on bone densitometry. Section 4.3.10 states that in cases of uncertainty, a DXA can be performed to confirm osteoporosis. It would be more appropriate to advocate BMD measurement in all older women with an osteoporotic fracture, unless the clinician is confident that the fracture followed only minimal trauma.

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